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Subclinical cardiac stiffness is associated with arterial stiffness in healthy young nulligravid women: Potential links to preeclampsia

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ABSTRACT

Objectives: Preeclampsia is an independent risk factor for subsequent cardiovascular disease and diastolic dysfunction and has been linked to arterial stiffness. We hypothesized that arterial stiffness would be associated with echocardiographic markers of diastolic dysfunction in healthy nulligravid women.
Study design: 31 healthy nulligravid women underwent assessment of peripheral arterial stiffness via aorto-femoral pulse wave velocity, popliteal distensibility and β stiffness measures as well as hemodynamic response to volume challenge. 22 underwent cardiac assessment via conventional and stress echocardiography with a focus on diastolic function utilizing tissue/pulse wave Doppler imaging and 3D speckle tracking. Bivariate associations between variables were evaluated using correlation coefficients (Pearson r) and Student's *t*-tests.
Results: No participants had echocardiographic values meeting criteria for overt diastolic dysfunction. Baseline global circumferential strain was significantly correlated with distensibility and β stiffness ($n = 18$, $r = -0.61$, $p = 0.007$, $n = 18$, $r = 0.56$, $p = 0.01$). Peak deceleration time was correlated with β stiffness ($n = 9$; $r = 0.80$, $p = 0.01$). Pulse wave velocity was not significantly correlated with cardiac measures ($p > 0.05$). Family history of a first or second degree relative with myocardial infarction or hypertension was associated with decreased popliteal artery distensibility ($p = 0.02$ and $p = 0.03$, respectively).
Conclusions: In healthy nulligravid women there is evidence that markers of decreased left ventricular relaxation are associated with increased peripheral vascular stiffness as is a family history of myocardial infarction or hypertension. These findings raise the possibility that the diastolic dysfunction and arterial stiffness observed in the setting of preeclampsia are driven by underlying properties present prior to pregnancy and contribute to lifetime cardiovascular risk.

1. Introduction

Preeclampsia as defined by new onset hypertension after 20 weeks gestation in association with end organ injury complicates approximately 5% of pregnancies [1]. In the United States, the incidence has increased by as much as 25% over the last two decades and is a leading cause of maternal morbidity worldwide [2]. The acute complications have been well described and there is mounting evidence that preeclampsia has a significant association with long term cardiovascular morbidity including hypertension, ischemia, thrombosis and cardiac dysfunction [3–8]. In the context of women's longitudinal health, clarifying both the underlying risk factors for the development of preeclampsia as well as the independent long term cardiovascular consequences of this disorder are central to understanding preeclampsia's association with women's cardiovascular health and its promotion.

Current hypotheses for the causality of preeclampsia focus on an early sequence of placentally derived abnormalities that when combined with maternal systemic responsiveness can manifest into the classic picture of endothelial injury, proteinuria and hypertension. However, there is evidence that the pathophysiologic sequence of preeclampsia might result from impaired cardiovascular adaptation to the physiologic challenge of pregnancy when it is superimposed on a

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predisposing pre-pregnancy phenotype [9–12].

Clinically, cardiovascular risk factors such as serum lipids and systolic blood pressure as well as differences in cardiac output, peripheral resistance and mean arterial pressure in the preconception period have been associated with increased risk for preeclampsia and growth restriction [11,12]. The concept of pre-pregnancy susceptibility to cardiovascular dysfunction within pregnancy suggests that cardiovascular stiffness leads to an intolerance of volume expansion and that this serves as a pathophysiologic pathway to clinical preeclampsia [13–16]. In the non-pregnant population, subclinical abnormalities in cardiac, peripheral vasculature function and hemodynamic response to volume loading clearly play a role in long term stratification of cardiovascular risk [17]. The persistent diminished diastolic function and abnormal left ventricular geometry in preeclamptic women may be representative of disproportionate remodeling in the setting of underlying propensity to develop cardiovascular disease, and represent a shared vascular pathway between long term cardiovascular disease and preeclampsia [4,7,8,18,19].

It is our current theory that the cardiac dysfunction observed with preeclampsia, as well as the underlying risk for future cardiac disease may be detectable in the pre-pregnant state and contributes to the clinical presentation of preeclampsia and its long-term associations. By understanding baseline differences in cardiac structure and function that are linked with these findings we hope to further identify potential pre-pregnancy predictors that could translate into a risk assessment for preeclampsia and subsequent cardiovascular disease. Specifically, in the current study we hypothesize that increased vascular stiffness will be associated with echocardiographic markers of diastolic dysfunction in healthy, normotensive nulligravid women.

2. Methods

With a prospective observational cohort design, recruited subjects underwent a screening process to determine study eligibility and were comprised of 32 healthy, 18–37-year-old nulligravid women, defined as no prior clinically recognized pregnancies. At the time of enrollment, women had regular menstrual cycles or were using levonorgestrel intrauterine device. Use of systemic hormonal contraception was exclusionary. Additional exclusion criteria included active smoking, body mass index greater than 40, significant medical diagnoses with associated medication use such as hypertension, diabetes, seizure disorder or poorly controlled asthma and thyroid disorders. Women were enrolled over a ten-month period from August 2016 to June 2017. Protocol approval was obtained through the University of Vermont Human Investigational Committee and written informed consent was obtained from all participants. Data collection took place in a single day within the University of Vermont Clinical Research Center.

Prior to the day of the study, subjects abstained from alcohol, nonsteroidal and decongestant use for 48 h and caffeine for 24 h. On the morning of the study subjects were in a fasting state and if cycling regularly were scheduled during the follicular phase of the menstrual cycle to avoid potential hormonally driven vascular changes. Abstinence as noted above was also confirmed.

After ensuring a negative urine pregnancy test, basic medical and surgical histories were confirmed as well as family history focused on hypertension, diabetes, stroke, myocardial infarction and preeclampsia. Height, weight, pulse, respiratory rate and seated blood pressure measures were obtained.

Serum was obtained via venipuncture and bone mineral density using dual X-ray absorptiometry via the GE Lunar Prodigy Encore fan-beam densitometer (version 16) with Corescan Software (GE Healthcare Lunar, Madison, WI), was performed for future analysis. Body mass index and fat percentage were obtained to characterize baseline characteristics of the cohort.

3. Vascular assessment

Vascular assessment was performed using a Vivid 7 ultrasound unit (GE Medical, Milwaukee, WI) equipped with probes for cardiac, abdominal and peripheral vascular measurements. Baseline cardiac output (mL/min) was determined by brief echocardiographic examination as a product of pulse and stroke volume, calculated using left ventricular outflow area and mean systolic velocity [20,21].

Arterial stiffness was evaluated with multiple parameters including using pulse wave velocity, distensibility and β stiffness index of the popliteal artery. Our measure of pulse wave velocity (PWV) was between the aortic root and the popliteal artery, a large vessel concourse consistent with the established standard for PWV of carotid to femoral [22]. Pulse wave velocity was performed using a 10 MHz transducer [23,24]. Multiple popliteal pulse waveforms were acquired and time from R wave to peak systolic flow, relative to the distance from the heart to the popliteal artery was used to establish the pulse wave velocity. To determine distensibility and β stiffness index, ultrasound and continuous blood pressure monitoring were used to obtain baseline vessel diameter measurements as well as diameter change through the cardiac cycle along with associated changes in supine blood pressure. Distensibility was calculated (Distensibility = $\Delta D/\Delta PDd$) with decreasing values indicating stiffer arteries. β stiffness index was calculated using β stiffness ($\beta = n(Ps/Pd)\ Dd/\Delta D$), with increasing values indicating stiffer arteries [25]. Values for both were an average of multiple measurements.

Assessment of vascular compliance was performed using a volume challenge designed to mimic the volume expansion of pregnancy. Subjects received an intravenous infusion of 500 mL normal saline with concomitant continuous non-invasive blood pressure monitoring on the contra-lateral arm. After baseline measurement and machine calibration of the Finometer PRO (Finopres Medical Systems, Enschede, Netherlands) infusion took place over 10 min followed by an additional 15 min of continuous cardiac monitoring following completion for a total of 25 min of hemodynamic observation.

4. Cardiac assessment

Participants underwent resting electrocardiogram followed by resting echocardiography using a Phillips EPIQ 7 ultrasound. Exercise stress testing was performed using an upright stationary bicycle starting with a workload of 25 W (W) with 5 W increments every minute for a goal heart rate of 130 bpm or symptom onset [26]. Once target heart rate was reached, the workload was maintained for 3 min at which time echocardiography was repeated. Three minutes following cessation of exercise, echocardiography was again performed. At each stage of echocardiography, standard parasternal, apical, and subxiphoid views were obtained. Tissue Doppler and pulse wave imaging of mitral inflow velocities were obtained according to American Society of Echocardiography guidelines specifically evaluating peak mitral annular velocity during early filling (e′), early (E) to late (A) ventricular filling velocities, interventricular relaxation time (IVRT), and deceleration time (DT) [27]. 3D speckle tracking analysis was performed offline using TOMTEC Imaging Systems Version 4.6.3.9 (4D LV-Function) for evaluation of global longitudinal strain (GLS), global circumferential strain (GCS), and radial strain [26–29].

Statistical evaluation was based on correlation analyses utilizing Pearson's r and Student's *t*-tests. Statistical analysis was performed using SAS statistical software (SAS Institute, Cary, NC) with statistical significance determined based on $\alpha = 0.05$.

5. Results

Of the 31 patients, 22 underwent echocardiography. Baseline characteristics are listed in Table 1. Participants were on average 26 ± 4.1 years old with mean body mass index of 22.9 ± 3.6 kg/m^2.

Table 1
Participant characteristics.

Baseline Characteristics		Mean ± SD or n (%)
Age (years)		26 ± 4.1
Race	White	25 (81%)
	Non-white	6 (19%)
Body Mass Index (kg/m^2)		22.9 ± 3.6
Body fat (%)		30.5 ± 6.4
Systolic Blood Pressure (mmHg)		106 ± 10.1
Diastolic Blood Pressure (mmHg)		67 ± 7.4
Mean Arterial Pressure (mmHg)		80.0 ± 7.6
Cardiac output (L/min)		4.36 ± 0.97

Family history of first or second degree relative with myocardial infarction was present in 13/31 (42%) and family history of hypertension was present in 24/31 (77%).

As anticipated, no overt diastolic dysfunction was observed in any of these heathy participants. Global circumferential strain, a contemporary tool used to evaluate ventricular relaxation has a reported normal range of −18 to −25% [30]. Lesser negative values are more indicative of early diastolic dysfunction with a threshold of −15% utilized for clinical heart failure and diagnostic purposes [27]. In our study, baseline global circumferential strain (GCS) ranged −24.5 to −37.1% with a mean of 32.5 ± 2.8%. The mitral inflow signal is used to evaluate left ventricular filling pressures with longer deceleration times reflective of diminished relaxation. General population mean is around 166 ms with ≥240 ms used as a cutoff for abnormal diastolic function [31]. Peak stress deceleration time ranged 54–151 ms in our participants with a mean of 100 ± 27.9 ms. In the popliteal artery, the normal range for distensibility has not been established in healthy participants. In our study, popliteal artery distensibility ranged 0.0002 to 0.003 ± 0.0006 kPa^{-1} with a mean of 0.0009 ± 0.0005 kPa^{-1}. β stiffness index ranged 4.05–83.0 with a mean of 19.77 ± 17.8. In carotid atherosclerosis literature, a cutoff of 13 has been used to indicate abnormal elasticity [25].

Distensibility and β stiffness index were both associated with baseline global circumferential strain (n = 18, r = −0.61, p = 0.007, n = 18, r = 0.56, p = 0.01, respectively Fig. 1). β stiffness index was also associated with peak stress deceleration time (n = 9; r = 0.80, p = 0.01, Fig. 2) and while distensibility was not significantly associated with peak deceleration time, moderate correlation was observed between the two measures (r = −0.66, p = 0.05).

Baseline circumferential strain was not significantly associated with popliteal pulse wave velocity (n = 18, r = −0.12, p = 0.63), pulse pressure response to volume challenge (n = 17, r = 0.001, p = 0.99) or MAP response to volume challenge (n = 17, r = −0.003, p = 0.99). Peak deceleration time was not associated with popliteal pulse wave velocity (n = 9, r = −0.20, p = 0.6), pulse pressure response to volume challenge (n = 9, r = 0.17, p = 0.66) or MAP response to volume challenge (n = 9, r = −0.23, p = 0.55).

When examining women with family histories of a first or second degree relative with either myocardial infarction or hypertension compared to those without such family histories, a significant difference in mean popliteal artery distensibility was noted (0.0007 ± 0.0003 vs. 0.001 ± 0.0006 kPa^{-1}, *t*-test, p = 0.02 for myocardial infarction, 0.0008 ± 0.0004 vs. 0.001 ± 0.0007 kPa^{-1} *t*-test, p = 0.03 for hypertension, Fig. 3). No significant differences were noted between those with and without a family history of myocardial infarction for β stiffness index (23.0 ± 19.9 vs. 16.9 ± 16.2, *t*-test, p = 0.29), pulse wave velocity (3.71 ± 0.4 vs. 4.03 ± 1.1 m/s, *t*-test, p = 0.34), mean arterial pressure response to volume (122 ± 101 vs. 134 ± 72 mmHg, *t*-test, p = 0.73), or pulse pressure response to volume (91.6 ± 124.2 v. 78.5 ± 89.8 mmHg, *t*-test, p = 0.76). Similarly, no significant differences were noted between those with and without a family history of hypertension for β stiffness index (21.4 ± 18.2 vs. 14.1 ± 16.3 mmHg, *t*-test, p = 0.34), pulse wave velocity (3.95 ± 1 vs. 3.75 ± 0.5 m/s, *t*-test, p = 0.61), mean arterial pressure response to volume (125 ± 91 vs. 140 ± 68 mmHg, *t*-test, p = 0.73) or pulse pressure response to volume (84.6 ± 106 vs. 84.5 ± 111.6 mmHg, *t*-test, p = 0.99).

6. Discussion

Given the prevalence of preeclampsia and the implications for maternal cardiovascular health both acutely, in the perinatal period, as well as long term, the ability to identify predisposing characteristics prior to reproduction could have a significant effect on both prenatal care and general health maintenance. Our intent was to elucidate baseline characteristics and potential relationships between peripheral vasculature and cardiac physiology outside the context of pregnancy which could in turn be the basis for future studies focused on preeclampsia.

In reviewing normal pregnancy physiology, cardiovascular adaptation must occur to accommodate increased volume status [20,21,32,33]. The peripheral vasculature remodels to allow for the large physiologic increases in plasma volume, without a simultaneous

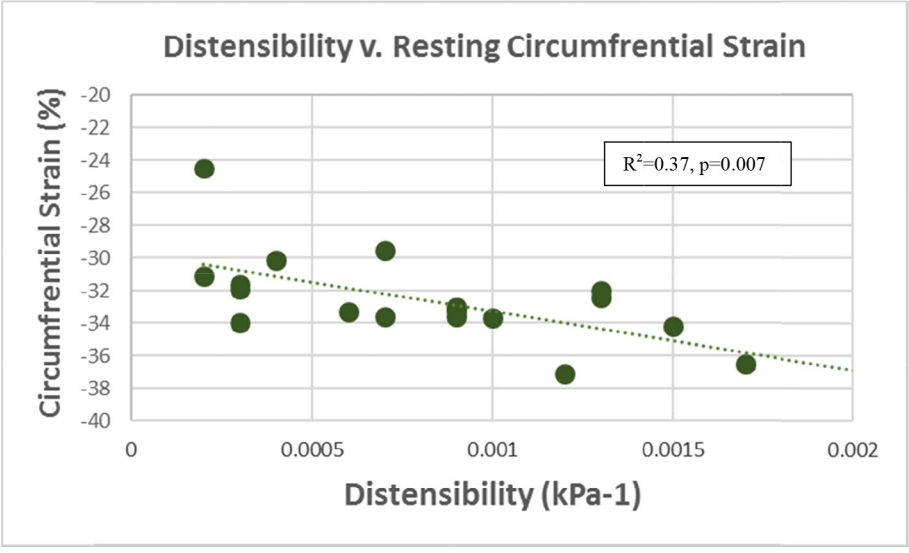

Fig. 1. Scatterplot of popliteal distensibility versus baseline circumferential strain.

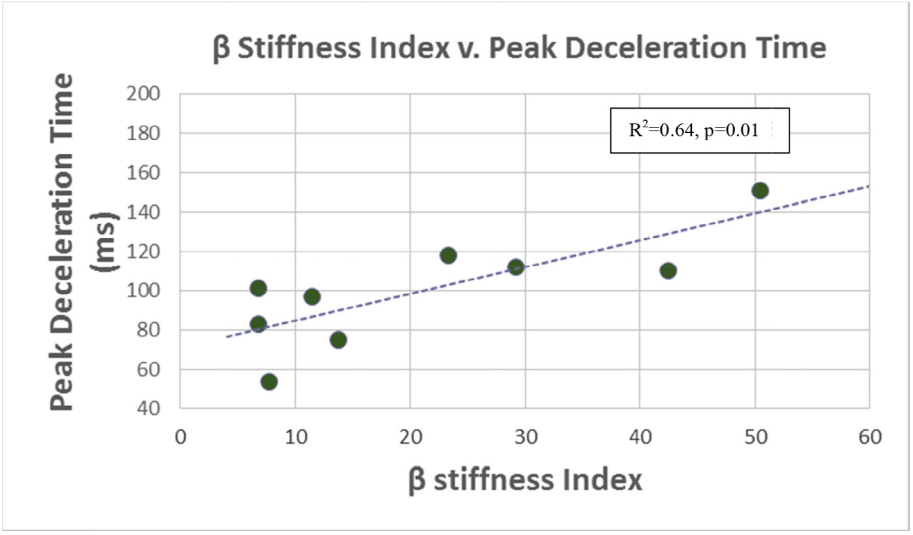

Fig. 2. Scatterplot beta stiffness versus peak deceleration time.

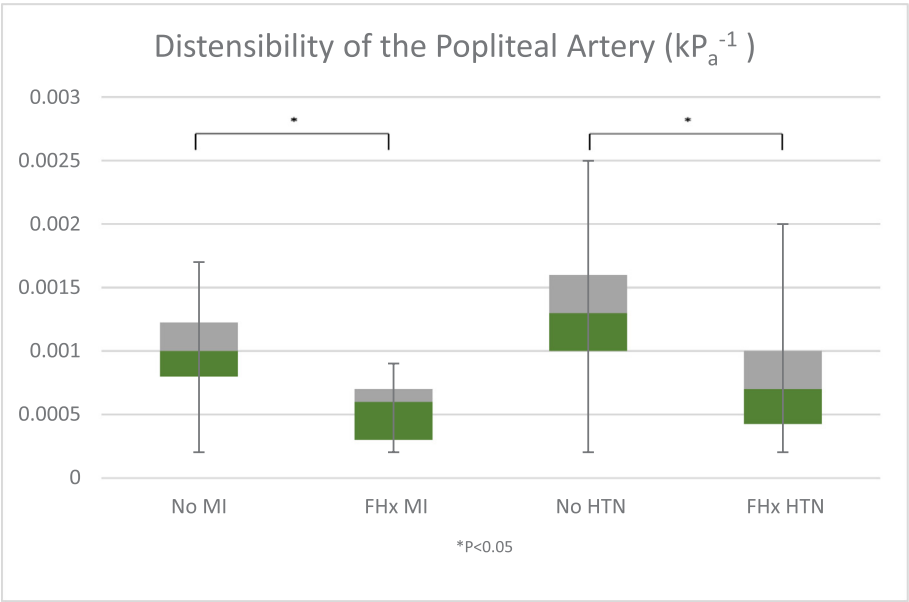

Fig. 3. Popliteal artery distensibility in women with and without a family history of cardiovascular disease.

increase in intravascular pressure (i.e. blood pressure). Normal cardiac remodeling, primarily an eccentric enlargement of the left ventricle, is a critical component permitting increased cardiac output and arterial compliance which outside of pregnancy would result in cardiac decompensation [32,34–37]. In preeclampsia, cardiac remodeling and physiology demonstrate a global diastolic dysfunction in the setting of asymptomatic left ventricular dysfunction, with similarities to heart failure with preserved ejection fraction (HFpEF) while peripheral vessels have increased stiffness consistent with the inability to accommodate increased volume loading and filling pressures [6,8,13,14,17,18,27,38–42].

Evidence has demonstrated that while healthy pregnancy can mitigate cardiovascular risks later in life, a complicated pregnancy is associated with an increase in these risks. Specifically, regarding death from cardiovascular disease, women with a history of term preeclampsia have about a 1.5-fold increased risk which those with prior preterm preeclampsia this risk is increased eight-fold. The range of cardiovascular morbidity linked to preeclampsia is broad and includes hypertension, hemorrhagic stroke, heart failure, ischemic heart disease, angina, and thromboembolism [3–8]. Recurrence of preeclampsia has a seven-fold increased risk for cardiovascular disease as compared to a single episode, representing a dose dependent relationship. Prior evidence has shown that when controlling for pre-pregnancy hypertension, diabetes and other known risk factors, the increased risk for subsequent cardiovascular disease related to a history of preeclampsia persists, indicating an independent contribution to risk profile [43].

Asymptomatic structural and functional abnormalities in cardiac function, also classified as heart failure stage B, have been observed in women with a history of preeclampsia with a prevalence estimated as high as one in four [7]. These changes have been noted not only in the postpartum period, but also persisting into both the early and later years following pregnancy [7,44]. In a longitudinal, study looking at the years one to four following preeclampsia, 23% of women were noted to have features of stage B heart failure and while over 60% of women had resolution of cardiac findings over the course of two years, 19% had new development of findings [7]. Looking at asymptomatic heart failure more remote from delivery, data from a cohort of formerly preeclamptic women demonstrated that four to ten years post-

pregnancy, women had a 3.5 fold higher prevalence of asymptomatic stage B heart failure as compared to women without preeclampsia, which appeared to be independent of other shared cardiovascular risk factors [44].

There is evidence that prior to pregnancy, women with less compliant vasculature have an increased risk for development of preeclampsia and this susceptibility, influenced by differences in cardiovascular function, is the basis for examining this nulligravid population of healthy women exploring both peripheral vessel and echocardiographic studies [10–12,17].

Regarding our utilization of the popliteal artery, in a prior study we learned that the uterine artery response to sildenafil was more closely associated with flow mediated vasodilation in the popliteal artery than in the brachial artery [45]. Perhaps not surprising given the more common embryologic origins for the lower extremity and uterine circulations. Given this finding and our interest in the implication of vascular dysfunction for future pregnancy complications including abnormalities of uterine perfusion, we chose to evaluate the functional capacity of the popliteal rather than other easily accessed and imaged vessels.

Echocardiographic tools used to assess diastolic dysfunction in the adult population include measures reflective of ventricular filling pressures and myocardial relaxation and function. In addition to standard 2D and pulsed wave Doppler, tissue Doppler and strain analysis, a tool to evaluate regional myocardial contractility in three-dimensions, used in combination with exercise stress testing represent a comprehensive means to evaluate diastolic function [27,28]. Typically the application of these specific echocardiographic measures of diastolic dysfunction is in a higher risk cohort comprised of individuals middle aged or older with a predominance of male subjects. Few studies focus on women, especially young asymptomatic individuals for baseline evaluation.

The results of our study demonstrate parallels between stiffness in the periphery with that found in the heart. Specifically, baseline circumferential strain, a marker of myocardial dysfunction and left ventricular stiffness was correlated with popliteal distensibility and β stiffness index, two measures of local vessel elasticity. Peak exercise mitral deceleration time, a marker for left ventricular filling pressure and ventricular relaxation, was correlated with β stiffness index as well, demonstrating that increasing filling pressures are associated with stiffer vessels. These two echocardiographic markers have been used in evaluation of diastolic function.

Not unsurprisingly we did not identify overt diastolic dysfunction in this young healthy group of women. However, in the young women evaluated prior to any pregnancy there was evidence that markers of decreased left ventricular relaxation and myocardial function were associated with increased peripheral vascular stiffness. Specifically, assessment of diastolic function revealed relationships between strain analysis, a measure of myocardial contractility and pulsed wave Doppler of mitral deceleration time, reflective of left ventricular filling pressure and compliance and local popliteal artery stiffness indices [27]. We propose that these findings raise the possibility that the diastolic dysfunction observed in the setting of preeclampsia is driven by underlying properties present throughout the cardiovascular system, both central and peripheral, that may be present in the pre-pregnancy state.

Additionally, we identified in this cohort that in young women with no personal health history of cardiovascular disease, that a positive family history of either hypertension or myocardial infarction was correlated with a stiffer, less distensible popliteal artery. This finding suggests that subclinical differences in vessel physiology are present prior to reproduction and are also likely to be familial in their influence, contributing to lifetime cardiovascular risk profile. If certain cardiovascular characteristics that predispose to the development of preeclampsia and/or peripartum cardiomyopathy could be identified prior to reproduction then there remains the potential for improved screening, prenatal care and counseling of both short and long term health risk.

Strengths of this study include the interrogation of diastolic function and local arterial elasticity in a cohort of young women, a population in which there is less data regarding cardiovascular health. Furthermore, all participants were nulligravid, eliminating any influence on the cardiovascular system related to pregnancy exposure. Participants were not under systemic hormonal influence and were studied in the follicular phase removing some of the influence of hormonal milieu on the vasculature. Limitations include small sample size, healthy women with average BMI 22, primarily of Caucasian race somewhat limiting its generalizability. Due to difficulty with concurrent imaging during rigorous exercise on the upright bicycle, fewer patients had interpretable peak stress echocardiographic results than planned.

Stemming from this pilot study, future directions include follow-up of study subjects with a subsequent pregnancy with evaluation for the development of hypertensive disorders as well as a prospective cohort study assessing pre-pregnancy cardiovascular characteristics, specifically diastolic function and peripheral vascular stiffness, examining their influence on adverse pregnancy outcomes, including preeclampsia, in a future pregnancy.

7. Institution where research performed

University of Vermont, Burlington, VT.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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